Docket No.: 267344US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Takayuki FURUISHI, et al.

GROUP: 1626

SERIAL NO: 10/527,062

EXAMINER: GRAZIER, N.

FILED: March 9, 2005

FOR: PROLINE ESTER AND PREPARATION CONTAINING THE SAME FOR PERCUTANEOUS ADMINISTRATION

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes Kunihiro Minami who deposes and states that:

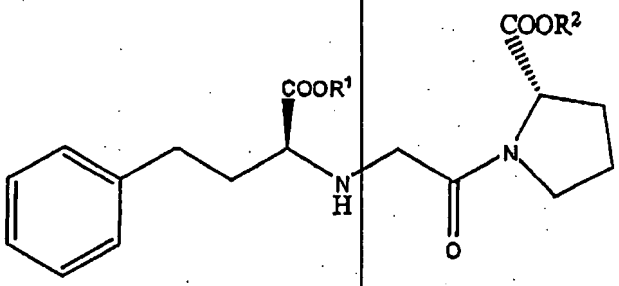
1. I am a graduate of Graduate School of Pharmaceutical Sciences and received my doctoral degree in the year 1998.

2. I have been employed by TOAEIYO LTD. for 9 years as a Research Scientist in the field of Pharmaceutical Technology.

3. That I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.

4. The following experiments were carried out by me or under my direct supervision and control.

5. Test molecules were produced by making the particular substitutions shown in the table below at positions R^1 and R^2 in the following chemical formula:



6. These test molecules were tested for the ability to permeate skin (skin permeability) and for stability using the following test procedures.

7. Skin permeability (IPM solution)

The same procedure as in "hairless mouse skin permeability test" described in Example 8 of the specification was performed, except for using IPM (isopropyl myristate) solution of each test compound instead of the patch formulation.

Specifically, 23g of each test compound was dissolved in 10 mL of IPM. Extirpated skin from dorsal region of hairless mouse was placed in a vertical diffusion cell filled with PBS, and left at 37°C for 1 hour. One milliliter of the solution of test compound was applied to 1.77cm^2 skin area. Subsequently, PBS in the receptor phase of the cell was collected and the concentration of test compound, enalapril and enalaprilat therein were measured with HPLC, as in Example 8.

8. Stability

The procedure used in the "Stability test" described in Example 6 in the present application was performed.

9. The results from the above-described skin permeability and stability tests are shown in the table below:

Compound		R1 (Core)	R2 (Proline)	Skin permeability (IPM solution)			Stability (%, storage at 60℃ for 1 week)		
				Permeation delay time (hr)	Skin permeation rate (μg/cm²/hr)	Presence ratio (24hr)*	Unchanged product	Closed ring product	Other degraded product
Inventive compound	1	-H	$-C_2H_4OH$	10.10	3.21	49.4 / 0.0 / 50.6	91.8	0.0	8.2
	2	-H	$-C_3H_6OH$	10.16	5.25	16.9 / 0.0 / 83.1	96.7	0.0	3.3
	3	-H	$-C_4H_8OH$	5.98	11.97	46.8 / 0.0 / 53.2	94.4	0.0	5.6
	4	-H	$-C_2H_4OMe$	3.26	14.95	43.9 / 0.0 / 56.1	99.1	0.0	0.9
	5	-H	$-C_2H_4OC_2H_4OMe$	4.56	11.47	48.0 / 0.0 / 52.0	94.2	0.0	5.8
Comparative compound	1	-H	-Me	4.20	0.73	20.8 / 0.0 / 79.2	100.0	0.0	0.0
	2	-H	-Et	4.24	0.93	32.7 / 0.0 / 67.3	100.0	0.0	0.0
	3	-Et	-Me	1.42	1.68	3.8 / 91.7 / 4.5	98.3	1.7	0.0
	4	-Et	-Et	-3.47	0.88	8.9 / 91.1 / 0.0	99.4	0.6	0.0
	5	-Et	-nPr	8.52	0.49	0.0 / 88.6 / 11.4	99.2	0.8	0.0
	6	-Et	-nBu	10.98	0.27	0.0 /100.0 / 0.0	99.5	0.5	0.0
	7	$-CH_2OCOMe$	-H	1.46	7.36	—	0.4	38.7	60.8
	8	$-CH_2OCOEt$	-H	3.76	21.77	—	0.0	45.2	54.8
	9	$-CH_2OCOnPr$	-H	1.95	46.07	—	0.0	34.6	65.5
	10	$-CH_2OCOtBu$	-H	3.90	16.16	0.0 / 0.0 /100.0	1.8	13.8	84.4
Enalapril		-Et	-H	1.28	45.14	0.0 / 97.1 / 2.9	0.0	48.4	51.6

* Concentration ratio (prodrug/enalapril/enalaprilat) in the receptor at 24 hrs after application

10. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

11. Further deponent saith not.

Kunihiro Minami
Signature

June 7, 2007
Date

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(OSMMN 05/06)